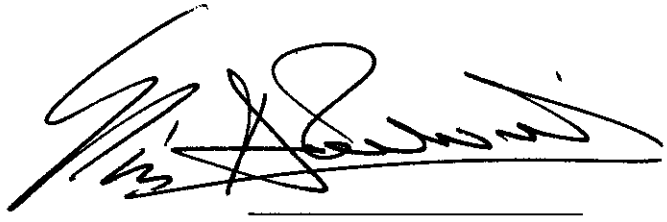
DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Neurological Disorders and Stroke

PARKINSON'S DISEASE RESEARCH AGENDA



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March 2005

Department of Health and Human Services

National Institutes of Health

National Institute of Neurological Disorders and Stroke

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PARKINSON'S DISEASE RESEARCH AGENDA

Executive Summary

In Senate report No. 108-345, p. 171, the Senate Committee on Appropriations requested that the National Institutes of Health (NIH) report on its implementation of the Parkinson's Disease (PD) Research Agenda, and to develop a conference to examine the path to a cure, working with patient advocacy, scientific, and non-profit communities.

The NIH continues to actively implement the PD Research Agenda, which has allowed it to engage the most productive and insightful scientists towards a cure for PD. The National Institute of Neurological Disorders and Stroke (NINDS) and fourteen other NIH Institutes and Centers have provided significant support to this community, which has enabled them to make significant progress towards improving our understanding of PD, and most importantly, towards developing new therapies for this disorder.

From a clinical perspective, the NIH continues to support research to improve deep brain stimulation – a treatment that is already helping thousands of people with PD, and was based on NIH-supported investments in neural circuitry and electrode development. NIH has also responded to needs identified in the PD Research Agenda by initiating a large phase II trial of potential neuroprotective therapies. An extensive evaluation program preceded the selection of the drugs used in the first four studies; any of these compounds that prove successful in the first study will be considered for a phase III trial. Multiple other clinical studies complement these efforts in neuroprotection, including studies to explore interventions that may improve swallowing, and to assess compounds that can alleviate depression – all of which are relevant to individuals with PD.

NIH is also committed to improving the pipeline of therapies from basic science into the clinic. As one successful example, NINDS has funded a working group of investigators to develop a clinically-appropriate method for treating PD using gene therapy. This group has made excellent progress in achieving its milestones, and it hopes to bridge the basic science in this field with a phase I clinical trial. NINDS has coupled specific awards like this to a larger series of Program Announcements specifically designed to enhance translational research at the Institute.

In addition to clinical and translational investments, the NIH-funded basic science research portfolio continues to span a substantial array of fields, from intramural

researchers making impressive progress in understanding PD genetics, to a cadre of extramural scientists exploring the cell biology of the disease, and large collaborative efforts across centers designed to improve our knowledge of the role of the environment in PD. NIH fully expects that the support of these studies now will translate into preventative strategies and treatments in the future.

All of this research is complemented by improvements in PD research infrastructure, which include the development of a Stem Cell Characterization Unit at the NIH, which is characterizing an array of federally-approved stem cell lines; a DNA repository that is reaching its pre-planned limit on deposits earlier than expected because of its popularity among the PD research community; and the recent establishment of a Data Organizing Center that will streamline the collection and use of clinical data across multiple PD research centers, including the Morris K. Udall Centers for PD Research and the Collaborative Centers for Parkinson's Disease Environmental Research.

These are just a few of the highlights that illustrate progress made since the start of the PD Research Agenda. Although scientists have not yet developed a cure for PD, they have pushed the field forward in many directions – all of which contribute to the eventual development of therapies. NINDS will continue to lead the efforts of the NIH in PD research beyond the Agenda towards this goal – utilizing the PD Matrix goals and other recommendations to be made by the scientific community at a June 2005 planning meeting to guide future program actions, from basic science initiatives to new clinical trials.

PARKINSON'S DISEASE RESEARCH AGENDA

Introduction

In its report for the Fiscal Year 2005 budget for the Department of Health and Human Services (HHS), the Senate Committee on Appropriations stated:

"Parkinson's Disease – The Committee commends the Director for his strong support and facilitation of collaboration with patient advocacy groups, health non-profits, and international organizations.

The Committee is also aware that the Parkinson's Disease Research Agenda [PDRA] developed by NIH in 2000 included professional judgments funding projections that totaled an additional $1,000,000,000 over 5 years to achieve a cure. The Committee strongly urges NIH to come as close as possible to fulfilling that Agenda while maintaining the standards of peer review. Furthermore, the Committee is also aware that the Director has prepared his own 'matrix' for Parkinson's which, while laudable, falls short of the ambitious goal of the Parkinson's Disease Research Agenda to find a cure for Parkinson's by developing a roadmap and projections of the resources needed to achieve that goal.

The Committee strongly urges the NIH to devote additional resources to Parkinson's research, as recommended by the Parkinson's disease Research Agenda, using all available mechanisms, including RFAs.

The Committee expects the NIH to report to Congress by April 2005, not only on the steps it is taking to fulfill the Parkinson's disease Research Agenda, but also its progress towards finding a cure for this devastating disease. Additionally, as 5 years have elapsed since the last NIH conference on Parkinson's disease, the Committee strongly urges the Director to hold another conference, similar to the one held in November 1999, to examine the path to a cure, working with patient advocacy, scientific, and non-profit communities. The results of the conference should produce a strategic plan setting forth the research funding and programs required to secure the earliest possible development of effective therapies, prevention, and a cure for Parkinson's disease." (Senate report No. 108-345, page 171)

The following report has been prepared by the National Institutes of Health (NIH) of the HHS in response to this request.

Background

In March of 2000, the NIH issued the Parkinson's Disease (PD) Research Agenda, a five-year plan outlining the most promising and crucial areas of research needed on this disease, so that scientific progress towards a cure would be expedited. While NIH recognizes that a permanent cure for PD has not been developed during the past five years, this plan has enabled NIH to engage the most productive and insightful scientists towards this goal, and has provided generous levels of funding to the research community in support of this effort. As a result, the scientific community has made significant progress towards improving our understanding of PD, and most importantly, towards the development of new therapies.

To assess progress at the midpoint of the PD Research Agenda, NIH sponsored two meetings (which included members of the scientific and clinical communities, and in the first, representatives from PD voluntary organizations) to discuss relevant research findings and NIH-supported activities, and to make recommendations for future directions. The first meeting, held in January 2002, focused on scientific goals and an assessment of progress on the Agenda. The attendees agreed that in many areas of research, the NIH had taken an appropriate course of action and should continue its efforts. However, they also outlined six additional areas for research focus, including translational research, dopaminergic systems, non-dopaminergic systems (including non-motor complications), biomarkers and assessment tools, preclinical studies of gene therapy, and animal models of PD. Progress in many of these areas is illustrated in the highlights below.

At the second assessment meeting, the Parkinson's Disease Coordination Summit, held in July 2002, the NIH asked attendees to examine the NIH PD research portfolio in an international context, and to prioritize remaining roadblocks for PD researchers. The recommendations from this meeting formed the basis for a tangible Matrix of research and program management goals, to be achieved over a prescribed timeline. The Matrix continues to serve as a management tool for guiding NIH program activities, as well as collaborations with the PD voluntary community, and its design lends itself easily to ongoing assessment and revision as old goals are achieved and new goals are identified.

Since the initiation of the PD Research Agenda, hundreds of NIH-supported research findings have been published. However, this report will only present a snapshot of some of the most critical discoveries in clinical, translational, and basic research, and our ongoing program efforts to address existing roadblocks

and to move the field forward towards improving the health of individuals with PD.

Clinical Research

A Clinical Success Story for Advanced Patients

"Neurosurgical approaches are becoming increasingly important in the treatment of Parkinson's disease, including precision ablation therapies, deep brain stimulation, and cell transplantation... A wide range of studies are needed to understand how these interventions affect the brain, to improve the technologies involved, and to evaluate the results of the various approaches in patients." – The Parkinson's Disease Research Agenda

In 2002, the U.S. Food and Drug Administration approved the use of deep brain stimulation (DBS) for advanced Parkinson's, and to date, thousands of people worldwide have undergone this procedure. In successful cases, the improvement in a person's mobility can be dramatic – enabling people whose disease had advanced significantly to return to many normal activities. The use of surgical approaches to treat PD has evolved over many decades, through the work of clinicians both in the U.S. and overseas. However, NIH-supported studies of the brain circuits that control movement, specifically those involving a group of structures in the brain called the basal ganglia that play an important role in the clinical manifestations of PD, were particularly critical to this field. In addition, NIH funding was also instrumental in enabling researchers to study how interference with these circuits could improve parkinsonian symptoms in non-human primate models of the disease. This body of knowledge, coupled with advances from the NIH-supported Neural Prosthesis Program – which supported the development and refinement of electrodes to stimulate brain tissue – laid the critical groundwork for the ultimate success of DBS, and for the continued basic science and clinical studies of this approach.

Although the FDA has approved DBS for PD, research questions remain – and the answers to these questions will be critical to making further improvements in this therapy. To address these issues, the National Institute of Neurological Disorders and Stroke (NINDS) has been collaborating with the Department of Veterans Affairs (VA) since January 2002 on the largest trial to date of DBS in individuals with PD. The trial is designed in two phases – the first to compare DBS and best medical management, and the second to evaluate the effects of DBS in two different brain locations. NINDS is providing substantial support for this project, primarily to enhance the enrollment of women and minorities. Although

recruitment was more difficult than expected, the trial is moving ahead well, with enrollment of subjects due to end in April of 2005, and results on outcomes expected in early 2008.

Improving Options for Drug Therapy

"There are promising therapeutic interventions for Parkinson's disease which have not undergone the requisite studies for safety, tolerability and dose-response effects. These studies usually require less than 100 total research subjects to examine safety, tolerability and dose finding. The data emerging from such studies would be used to further assess the rationale and feasibility of carrying out more definitive Phase III trials." – The Parkinson's Disease Research Agenda

Treatments that are currently used for PD can reduce the symptomatic effects in many people, but these therapies become less effective over time, as the underlying disease progresses. For this reason, the identification of therapies that can slow or stop the progression of PD would be of tremendous benefit. To address this goal, in April 2003 NINDS launched the Neuroprotection Exploratory Trials in PD (NET-PD) – a major series of cooperative clinical studies designed to evaluate drug therapies that have the potential to slow the progression of PD.

Prior to the initiation of any phase II trials in NET-PD, NINDS undertook an extensive process of planning, infrastructure development, and rigorous review of candidate therapies. Specifically, a team of pharmacologists, clinicians, and clinical trial experts – including NINDS staff – developed specific criteria for the evaluation of potential therapies, including scientific rationale, blood-brain barrier penetration, safety and tolerability, and evidence of efficacy in animal models or humans. The team of reviewers solicited suggestions from scientists and clinicians in academia and industry, as well as patient and foundation groups, in order to identify as many potential therapies as possible. A Steering Committee for this trial selected a small number of compounds to be evaluated in pilot studies: minocycline (an antibiotic related to tetracycline), creatine (a common nutritional supplement and possible antioxidant), coenzyme Q10 (a health supplement and antioxidant), and GPI-1485 (a proprietary compound with growth factor properties). Fifty-one sites participated in the enrollment of individuals with early, untreated PD for these studies and recruitment was completed ahead of schedule. Initial results are anticipated in late 2005, and the NET-PD research group will proceed with phase III trials of drugs that show promise in these first four phase II studies. In addition, the compound evaluation team is already engaged in a second round of drug assessments, to provide an additional group of

therapies to consider if none of the initial compounds prove successful in the phase II studies.

In addition to NET-PD, NINDS is also making investments in ensuring that therapies used commonly in practice do not contribute to the worsening of disease. As an example, NINDS has also supported a large clinical trial designed to determine if treatment with L-dopa accelerates the progression of PD. Given the widespread use of L-dopa in clinical practice, a resolution to this issue would have a significant impact on the patient community. The results of this trial were published in December 2004; the clinical assessments suggested that L-dopa either slows the progression of the disease or has a prolonged positive effect on the symptoms. However, imaging data collected in the trial suggest that the drug could have a negative impact on dopamine neurons. Although the outcome of this study was not as clear-cut as the investigators and the Institute had hoped, the research community continues to explore options for continued research on this question. (The Parkinson Study Group, *The New England Journal of Medicine*, 2004, 351:2498-2508)

Improvements in Quality of Life

"Non-motor symptoms of Parkinson's disease may include cognitive and emotional difficulties, including dementia and clinical depression, serious sleep disturbances, visual hallucinations, sexual dysfunction, bowel and bladder problems, speech difficulties, swallowing problems and many other changes that seriously affect the quality of life." – The Parkinson's Disease Research Agenda

In addition to studies that target the cells and circuits that play a role in the development of PD, several NIH Institutes and Centers (ICs) are actively engaged in clinical research that has the potential to lead to direct improvements in the quality of life for individuals with PD.

For example, the National Institute of Mental Health (NIMH) extends its commitment to reducing the burden of mental illness and behavioral dysfunction to PD, which is frequently co-morbid with depression and other mood and cognitive disorders. The Institute is currently supporting studies of the enzyme COMT, which appears to play a significant role in the breakdown of dopamine in areas of the brain associated with cognition (as opposed to those associated with movement). Recent studies have shown that the effectiveness of COMT in degrading dopamine is dependent on a well-identified variation in the gene encoding for this enzyme, with one variant being far more active than the other. Researchers examining the effect of this variation in the COMT gene in PD found that those individuals with the low-activity variant performed worse on tests of

cognitive function than those with the high-activity variant, and that performance was further worsened by dopaminergic medication. They suggest that those people with the low-activity variant may accumulate a relative excess of dopamine in areas of the brain involved with cognition as the brain adjusts to dopamine levels falling in motor areas. This excess dopamine negatively affects cognitive function, and drugs designed to alleviate the motor symptoms of PD worsen the situation. This work implies that the primary effect of COMT inhibition in some individuals may be on cognitive rather than motor symptoms, and that optimal treatment may need to target specific brain regions and specific patient genetics (Foltynie T., et al., *Movement Disorders*, 2004,19(8):885-91).

The National Institute on Deafness and Other Communication Disorders (NIDCD) is currently supporting a randomized study of two interventions for liquid aspiration in individuals with PD. Liquid aspiration is the most common type of aspiration in older populations, especially those suffering from debilitation, dementia, and depression. In addition, pneumonia may develop as a consequence of aspiration and is the fifth leading cause of death in the U.S. among persons age 65 years and over. Current treatment involves either use of chin-down position with swallowing or use of thickened liquids in the diet, without any clear evidence supporting the use of one treatment over the other. This ongoing trial is comparing these two approaches, with the hope of using the results to improve nutrition and quality of life for people with impaired swallowing function, including many individuals with PD.

The National Center for Complementary and Alternative Medicine (NCCAM) continues to sponsor research on complementary and alternative medicine practices to treat PD and its accompanying symptoms – including depression. A significant number of individuals with PD experience depression, making therapies critically important. However, commonly prescribed antidepressants are often not appropriate for individuals with PD because some can exacerbate already compromised motor functions. To address this need, NCCAM is supporting a clinical trial to determine if S-Adenosylmethionine (SAM-e; sold as a dietary supplement) is a safe and effective therapy for depression in PD. This study is also investigating the underlying mechanism of SAM-e as it relates to depression and the motor function symptoms of PD. In addition to this work, NCCAM is also supporting research on trans-cranial magnetic stimulation for individuals with PD and severe depression, and an investigation of Chinese exercise modalities, such as T'ai Chi, to improve movement function in individuals with PD. NCCAM also is funding a study to determine if valerian, a medicinal herb, can ameliorate sleep disturbances commonly associated with PD, and whether the placebo effect could be used to enhance treatment as well.

The National Institute of Child Health and Human Development (NICHD) supports research on human development and the maintenance of health, including approaches to rehabilitation following injury or disease. Currently, the NICHD PD research portfolio includes a clinical trial designed to examine the usefulness of exercise in individuals with PD, specifically to aid them in improving the efficiency of their movements, balance, and functional abilities. The Institute is also supporting a clinical investigation designed to conduct a longitudinal assessment of impairments in motor, cognitive and emotional function and the accompanying disabilities in individuals with PD, to understand how these impairments contribute to disability.

The National Center for Research Resources (NCRR) Research Resource for Complex Physiologic Signals has also made major progress in advancing the basic and clinical understanding of PD. Interdisciplinary work using this multi-center resource has focused on developing new ways of measuring and modeling tremor and disturbances of gait, and scientists at the resource have investigated how these measurements change in response to different therapeutic interventions (e.g., medications, deep brain stimulation, exercise, etc.). Resource findings are also leading to the development of new clinical biomarkers based on the dynamics of walking, to enhance the measurement of disease progression and to facilitate high throughput testing of response to therapeutic interventions.

Lastly, the National Institute of Nursing Research (NINR) supports research promoting quality of life and quality of care in those with chronic illnesses, including PD. Research priorities related to PD have included understanding and easing symptoms, delaying the onset of disability, slowing disease progression, and caring for individuals at the end of life. NINR-supported research extends to problems encountered by patients, families, and caregivers, such as an evaluation of a skill training program to enhance coping strategies for family caregivers.

Translational Research

Gene Therapy and Other Approaches Advance Toward the Clinic

"In the long run gene therapy offers tremendous potential for Parkinson's disease and many other disorders. Although holding promise, gene therapy for Parkinson's disease requires systematic evaluation of various parameters before its utility as a clinical tool can become established." – The Parkinson's Disease Research Agenda

In October 2000, NINDS and the NIH Office of Rare Diseases held a workshop on "Gene Therapy for Neurological Disorders," focusing primarily on PD and lysosomal storage disorders as two conditions with clear potential to benefit from gene therapy approaches. Discussions among PD researchers at this meeting led directly to the formation of a group of interested researchers. NINDS facilitated an additional gathering of this group via a grant supplement, and the team – officially called the Parkinson's Disease Gene Therapy Study Group – received NINDS funding in September 2002 to conduct a large, multi-institution, multidisciplinary, preclinical investigation of both dopaminergic enzyme gene therapy and neurotrophic gene therapy in non-human primate models of PD. Goals of the project include comparisons of the different genes and the testing of different gene delivery approaches. Investigators are also evaluating the safety, toxicity, efficacy, and longevity of these delivery vehicles, as well as their ability to turn gene expression on or off as needed. NIH anticipates that by supporting a rational, coordinated and integrated approach to the development of gene therapy treatments for PD, researchers can achieve the ultimate goal of laying the groundwork necessary for an Investigational New Drug application to the U.S. Food and Drug Administration necessary to proceed to clinical trials in humans.

Now more than two years into the project, the Study Group's efforts remain on track. One of the most important hurdles to safe gene delivery in humans with PD was the generation of a gene delivery vehicle, or vector, that can turn delivery on and off in a controlled fashion. Study Group investigators examined three different molecular configurations of vectors to determine which, if any, showed promise for tight control of gene delivery. Although two of the vectors tested were "leaky" – in that gene delivery still occurred when the vector was theoretically turned off – one of the vectors showed considerable promise for further investigation. These findings were recently published (Jiang et al., *Gene Therapy*, 2004, 11:1057-1067), and were an important early milestone for gene therapy for PD. The researchers have accomplished their other first and second year milestones on time as well, including the creation of a stable colony of parkinsonian non-human primates. Next steps will include testing in these animal models.

Other translational approaches to treating PD include the evaluation of a vaccine in preclinical studies. Scientists at the University of Nebraska and their collaborators, supported by NINDS and NCRR, have had some initial success in manipulating the immune system to provide protection for degenerating neurons in a mouse model of PD. These researchers generated a vaccine by using a compound to stimulate the immune system in one mouse, and transferring cells from this animal to another that had been treated with a compound that would

cause parkinsonian effects. Vaccination resulted in an immune response that turned off inflammation, conferred protection against further neuronal injury, and increased production of nerve cell growth factors. Although there is no guarantee that vaccination will act in humans the same way that it acts in mice, the overall strategy for triggering the immune system to prevent neuronal death and its manifestation into PD is promising. (Benner et al., *PNAS*, 2004, 101: 9435-9440)

In addition to these specific areas of research, NINDS also released three general Program Announcements (PAs) in July 2002, to encourage applications on translational research in neurological disease. These PAs are designed to implement a program of cooperative agreements that will support milestone-driven projects focused on the identification and pre-clinical testing of new therapeutics, to recruit exploratory/developmental projects, and to enhance the Institute's support for the training of investigators in translational research.

Basic Research

Historically, the basic research funded by the NIH has made a difference to people with PD. As described above, past NIH investments in neural circuitry and prosthetics laid the groundwork for today's progress in treating PD with deep brain stimulation; and basic NINDS-supported research in brain anatomy and neurochemical systems has provided a foundation for improvements in dopaminergic therapy. Other basic science studies, such as those supported by the National Institute on Drug Abuse (NIDA), have increased our fundamental understanding of the dopamine system and its role in a range of neurodegenerative and neuropsychiatric disorders. Today's basic science research continues to span a substantial array of fields, from intramural researchers making impressive progress in understanding PD genetics, to a cadre of extramural scientists exploring the cell biology of the disease, and large collaborative efforts across centers designed to improve our knowledge of the role of the environment in PD. NIH fully expects that the support of these studies now will translate into preventative strategies and treatments in the future.

Advancements in Genetics and Cell Biology Herald Change for the Field
"Identifying genes that can cause Parkinson's disease is crucial for understanding the disease process, revealing drug targets, improving early diagnosis, and developing animal models that accurately mimic the slow nerve cell death in human Parkinson's disease. Beyond single genes, we must unravel the complex interactions between genetic predisposition and environmental

influences that cause most cases of Parkinson's disease." – The Parkinson's Disease Research Agenda

The discovery that mutations in specific genes can play a causative role in the development of PD brought a sea change to a field that had previously focused on environmental causes of the disease. When NIH drafted the PD Agenda, mutations in only two genes were known to be linked to Parkinson's disease: alpha-synuclein and parkin. Now, six genes have recognized links to PD, including alpha-synuclein, parkin, UCH-L1, DJ-1, PINK-1, and dardarin/LRRK2 – a gene recently identified by NIH intramural researchers. Moreover, emerging evidence suggests that additional unidentified genes may also be linked to PD. While only a small fraction of PD is attributed to genetic mutations, the proteins implicated through genetic discovery are important for the study of all cases of PD, by providing invaluable insight into the pathogenesis of the disease, and revealing potential points of intervention.

The following highlights illustrate a few of the advances achieved by NIH-funded researchers since the start of the Agenda.

<u>*Alpha-Synuclein*</u>
"New insights into the role of synucleins in the pathobiology of Parkinson's disease would accelerate discovery of more effective therapies and provide fresh research opportunities to advance our understanding of Parkinson's disease." – The Parkinson's Disease Research Agenda

In June 1997, intramural researchers from the National Human Genome Research Institute (NHGRI), collaborating with investigators from New Jersey, Greece and Italy, made the initial discovery that mutations in the alpha-synuclein gene could contribute to early-onset hereditary PD in an Italian kindred. British researchers and their NIH-funded colleagues also made a subsequent important finding in August 1997 that alpha-synuclein protein is a primary component of Lewy bodies – the abnormal cellular structures that are the hallmark of PD. In addition to providing an important clue to the cause of the hereditary form of PD, these findings also linked the hereditary and sporadic forms of the disease at the cellular level. Funding and program support provided during the PD Research Agenda enabled investigators to take this knowledge and expand it to a greater understanding of complex role of synuclein in PD, and the generation of synuclein-based animal models.

Researchers quickly found that mutant alpha-synuclein proteins could aggregate into strands called fibrils, which accumulate in the brains of individual with PD.

Although some speculated that this accumulation was a central player in the degeneration of dopamine neurons in affected people, it was also possible that one of the intermediate structures in the production of fibrils could have been the more damaging protein species. In 2001, NINDS-supported researchers at the Brigham and Women's Morris K. Udall Center of Excellence for PD Research explored this hypothesis, and found that both dopamine and L-dopa seemed to stabilize the intermediate (protofibrillar) form of alpha-synuclein, in a way that could promote the development of PD. This finding was not only helpful in the design of more effective treatments for PD, but it also helped to explain why long-term dopamine therapy can cause severe side effects. Although this research group has gone on to conduct studies suggesting that alpha-synuclein protofibrils could cause neuronal damage by producing pores – or holes – in the cellular membrane, these hypotheses continue to generate considerable discussion among investigators who are actively gathering data to further characterize this process. (Conway et al., *Science*, 2001, 294(5545):1346-9)

Intramural and extramural researchers from the National Institute on Aging (NIA), NINDS, and NHGRI have also collected data that suggests that abnormal levels of the alpha-synuclein protein can contribute to PD, even if the protein is the product of the normal alpha-synuclein gene. In 2003, these investigators found that select families with early-onset PD have a triplication of the alpha-synuclein gene on one chromosome, leading to an approximate doubling of the production of this protein. These data are consistent with the hypothesis that the "dose" of alpha-synuclein present in these individuals' brains is the primary cause of their PD (Singleton et al., *Science*, 2003, 302:841). In addition, this same group of NIA researchers has also demonstrated that people with the synuclein triplication (four copies of the gene instead of two) have twice as much blood synuclein as their unaffected brothers and sisters (Miller et al., *Neurology*, 2004, 62: 1835-8). This suggests that blood synuclein levels may serve as a critically needed biomarker for disease.

Given the important causative role of synuclein in PD, NINDS-supported researchers have also focused on the creation of synuclein-based animal models which might recapitulate the disease process, thereby providing critical tools for testing potential therapies. In 2003, NINDS-supported investigators demonstrated that as little as a two-fold increase in the expression of mutant forms of the alpha-synuclein gene causes a catastrophic disturbance in the ability of affected yeast cells to maintain a normal cellular distribution of the alpha-synuclein protein. Not only does the accumulation of mutant proteins pose a toxicity risk to the cell, but it also compromises the normal function of alpha-synuclein in critical cellular processes (Outeiro and Lindquist, *Science*, 2003, 302:1772-1775). This research

group was funded as a result of a joint RFA in FY2002 that involved multiple NIH Institutes and several private PD research organizations. The objective of the RFA was to support high-risk, high-payoff research, and the expansion of our understanding of synuclein using yeast as a model system beautifully illustrates the value of these studies. This research is now being continued at a Udall center in Boston.

In addition, NHGRI intramural researchers have created a transgenic mouse which carries the mutated human alpha-synuclein gene in addition to its own copy of the gene. These mice exhibit abnormal neuronal distribution of alpha-synuclein as well as neurological behavioral changes (Gispert et al., *Molecular and Cellular Neuroscience*, 2003, 24(2):419-29). When their own copy of the gene is removed, and only the mutated human form of the gene is expressed, the mice develop a neuropathy characterized by limb weakness and paralysis. The differences between the two behavioral outcomes suggests that the normal mouse copy of alpha-synuclein may play a protective role against the damaging effects caused by the presence of a mutant human form of the gene (Cabin et al., *Neurobiology of Aging*, 2005, 26(1):25-35).

NINDS-funded researchers have also contributed to the development of animal models by demonstrating that over-expression of normal or mutant human alpha-synuclein via gene therapy can induce progressive parkinsonian neurodegeneration and motor impairment in non-human primates. Importantly, cell death occurs more slowly than with MPTP (a toxicant routinely used to create a parkinsonian condition in these animals), providing a time course more comparable to that observed in humans. This model may be advantageous to researchers studying the causes and potential therapies for the disorder. (Kirik et al., *PNAS*, 2003, 100(5): 2884-2889)

These and other prior research studies suggest that increased expression and aggregation of the alpha-synuclein protein is neurotoxic and contributes to dopamine cell death observed in PD. However, an NIEHS-supported study using an animal model of PD suggested that increased amounts of alpha-synuclein may be an initial protective response to insult. The development of PD, then, could reflect the loss of defensive properties associated with this protein. Understanding the possible dual role of alpha-synuclein may enable strategies to selectively recruit the beneficial effects associated with this protein as a novel approach to treatment of PD. (Manning-Bog et al., *The Journal of Neuroscience*, 2003, 23(8):3095-9)

Although this body of work does not provide a definitive answer to the question of the role of alpha-synuclein in PD, the field has advanced considerably since the

start of the PD Research Agenda. The investigators referenced here, as well as numerous others, are continuing to improve our understanding of alpha-synuclein and its function – with the ultimate goal to develop interventional strategies that target the mechanisms that definitively lead to disease.

Parkin

"The parkin protein, for example, has been implicated in early onset forms of Parkinson's disease. Like the alpha-synuclein protein, the function of parkin is unknown... Goals for this research should include....Studies on the function of parkin, including its potential role in the ubiquitination pathway....Development of animal models, such as knockouts in mice, flies, or worms, to study the roles of parkin and UCH-L1." – The Parkinson's Disease Research Agenda

In 1998, Japanese researchers identified mutations in the parkin gene as being responsible for a rare early-onset form of PD. By 2000, researchers at the Johns Hopkins University Morris K. Udall Center had demonstrated that the parkin protein plays a role in the normal operation of the ubiquitin system, which breaks down damaged or misfolded proteins inside neurons. Specifically, it helps to target proteins for intracellular destruction by a structure called the proteosome (Zhang et al., *PNAS*, 2000, 97(24):13354-13359). Although most individuals with parkin mutations do not exhibit precisely the same cellular changes as those with sporadic PD (such as Lewy bodies – intracellular protein deposits that are a hallmark of the disease in humans), abnormalities in protein processing may be a common link between the various types of PD.

In an effort to stimulate research, the NINDS released a Request for Applications (RFA) in 2000 on the role of parkin in PD. A number of projects funded under this RFA have made critical contributions to our understanding of parkin biology, including the discovery that parkin can reduce the toxic effects of mutant alpha-synuclein or inhibitors of the proteosome in cultured dopaminergic neurons (Petrucelli et al., 2002, *Neuron*, 36:1007-1019); and the finding that normal parkin may be involved in the targeting of misfolded structural proteins for destruction (Ren et al., *The Journal of Neuroscience*, 2003, 23(8):3316-3324). This work is continuing within the intramural program at NIA. Two other grants awarded under this RFA involved the creation of animals lacking parkin, to enable the study of this gene in normal and disease states. In the first study, parkin mutations in fruit flies implicate mitochondria – the cellular energy generators – in affected systems (Greene et al., *PNAS*, 2003, 100(7): 4078-4083). In a second study, parkin-deficient mice exhibit normal brain structure and numbers of dopamine neurons, but display subtle abnormalities in dopamine system function and behaviors that rely on this system (Goldberg et al., *The*

Journal of Biological Chemistry, 2003, 278(44):43629-43635). Together, these data suggest that normal parkin may protect cells against an accumulation of misfolded proteins, and that while parkin mutations may not cause overt neural degeneration, they can affect dopaminergic neurons and may impair mitochondrial function.

The studies described above, and many others supported by NIH, have begun to clarify how parkin mutations could cause or contribute to the development of PD. However, many aspects of its participation in this disease are not completely understood, such as the complete cataloguing of molecules targeted for destruction by parkin; and the mechanism by which parkin mutations may contribute to the selective degeneration of dopaminergic neurons. NIH-funded researchers are committed to continuing research to address these issues.

Other Recent Genetic Discoveries

"Clearly, major priorities must be to discover other gene defects that can cause or increase risk for Parkinson's disease, to develop a more complete understanding of the role of these genes in parkinsonisms, and to use these genetic findings to make useful cellular and animal models of disease that would enable researchers to study the disease process and test new treatments." – The Parkinson's Disease Research Agenda

DJ-1: The DJ-1 gene, associated with a rare form of inherited, early-onset, parkinsonism, was identified in 2003. The function of the protein was not known at that time, however NIA researchers have since obtained data suggesting that the DJ-1 protein is neuroprotective, specifically that it may act as a signaling molecule that tells the mitochondria – the energy generators in the cell – that oxidative stress is present. Mutations in the DJ-1 gene may inhibit this signaling and impair the cellular response to oxidative stress in affected neurons. (Canet-Aviles et al., *PNAS*, 2004, 101: 9103-8)

PINK1: Intramural researchers at NHGRI have recently collaborated with groups from Italy, Spain and Germany to discover the gene for a recessive form of inherited PD. The gene, named PINK1 (Valente et al., *Science,* 2004, 304:1158-60) encodes a protein which is located in the mitochondria which may have a protective effect on these structures. It is hypothesized that mutations in both copies of the gene may eliminate this protective effect.

Dardarin/LRRK2: Intramural researchers from the NIA recently published the initial characterization of the gene responsible for PD in five families from England and Spain, termed dardarin (derived from the Basque word for tremor;

Paisan-Ruiz et al., *Neuron*, 2004, 44(4):595-600). This work was independently replicated by researchers from the Mayo Clinic Udall Center, who termed the gene LRRK2 (Zimprich et al., *Neuron*, 2004, 44(4):601-607). Although little is known about this gene at present, it does appear capable of causing late-onset forms of the disease, is expressed throughout the brain, and may function as a kinase – an enzyme that is capable of modifying proteins inside the cell that have been implicated in PD, such as alpha-synuclein and tau. Intramural scientists from NIA, in collaboration with NINDS funded scientists from Indiana and a group from the United Kingdom, have recently produced data that shows as much as two percent of sporadic PD cases may be caused by a single mutation in LRRK2 (Gilks et al., 2005, *The Lancet*, 365:415-416).

Impact of Progress in Genetics and Cell Biology

Taken in isolation, studies involving new gene discovery, or gene characterization, might not appear to be linked closely with clinical improvement for people with PD. However, the implications of this work are very relevant to the clinic. Genetic mutations in genes linked to PD and single nucleotide polymorphisms – subtle variations in the genetic code that occurs across a population – can help clinicians identify who is at risk for the disease. For example, researchers at NIDA have discovered a devastating and rare mutation of a gene called ADH1C (Buervenich et al., *Archives of Neurology*, 2005; 62:74-78), and have demonstrated that this mutation is strongly associated with PD in a large international sample. Researchers from NIDA's intramural research program are also collaborating with researchers from the Karolinska Institute in Sweden to conduct genetic analyses of Parkinsonian patients. They are using the candidate gene approach and case-control studies, to detect susceptibility genes. They have access to DNA from over 1000 non-related PD patients and nearly 1000 controls covering two continents and different geographic regions.

In addition, novel methods of gene mapping – including the use of combined genetic techniques to provide greater power to associate genes with disease – are already in use in NIH-supported laboratories. Researchers funded by the NIA have recently used the latter approach to identify specific regions on chromosome 10 that may be linked to the age of onset for both Alzheimer's disease (AD) and PD (Yi-Ju et al., *Human Molecular Genetics*, In Press). The study of families with rare known mutations that cause PD also facilitates the design and testing of early diagnostic tests for the disease.

As preventative therapies and neuroprotective treatments are developed, this information will play a critical role in minimizing disease progression. In addition, genetic mutations can provide a direct window into the cellular causes of

disease – for individuals in hereditary disease, and in some cases (such as alpha-synuclein) for individuals with sporadic late-onset disease as well. A therapeutic agent based on these commonalities may be successful for both forms of PD.

Parkinson's and the Environment

"Beyond single genes, we must unravel the complex interactions between genetic predisposition and environmental influences that cause most cases of Parkinson's disease." – The Parkinson's Disease Research Agenda

Until the discovery that mutations in the alpha-synuclein gene were present in some families with hereditary PD, a considerable number of researchers believed that PD was caused primarily by exposure to environmental agents. Today, it is thought that genetic predisposition and environmental exposures act together to cause many if not all cases of the disease. A number of important discoveries have been made since the initiation of the PD Agenda that shed considerable light on the extent to which toxic exposures may contribute to PD, and the pathways through which these agents may cause disease.

Development of the Rotenone Model

In December 2000, NINDS and NIA-funded researchers published the finding that chronic administration of the botanical pesticide rotenone to rats causes anatomical and behavioral changes that mimic those seen in PD (Betarbet et al., *Nature Neuroscience*, 2000, 3:1301-1306). The most exciting feature of this model is the appearance of Lewy bodies, which had not been observed in other animal models of PD. The similarity of the rotenone model to the human illness suggested that it could be of tremendous value to PD researchers as a tool to understand the cascade of cellular and molecular events that leads to death of dopamine neurons. In light of the potential importance of the rotenone model, the National Institute of Environmental Health Sciences (NIEHS) and NINDS have supported efforts to further develop and characterize this model, including improvements in the dosing schedule, and translation of this model into mice – which would allow for the manipulation of genes in addition to the rotenone exposure.

The rotenone model has already been extended successfully to nonrodent species. Some researchers have reported that rotenone administration creates parkinsonian features in fruit flies (Coulom and Birman, *Journal of Neuroscience*, 2004, 24:10993-10998). This latest work built on previous studies funded by the NIA and the NINDS to develop fruit fly models of human neurodegenerative disease (Feany and Bender, *Nature*, 2000, 404:394-398; Auluck and Bonini, *Science*, 2002, 295:865-868; Scherzer et al., *Human Molecular Genetics*, 2003, 12:2457-

2466; Greene J. et al., *PNAS*, 2003, 100:4078-4083; Pesah et al., *Development*, 2004, 131:2183-12194). The availability of a rotenone model in flies will enable researchers to capitalize on the large collection of genetic methods that have been developed for use in this species. In addition, preliminary data in nonhuman primates indicate that chronic exposure to low doses of rotenone can reproduce PD pathology in these animals.

Other Environmental Toxins

Rotenone is only one of several agricultural compounds that can have detrimental effects on the nervous system. The NIEHS has supported the development and characterization of another PD rodent model based on the combined chronic exposure to the agrichemicals paraquat and maneb. The combination of these chemicals produces synergistic effects on behavioral and neurochemical measures of dopamine function in brain. (Thiruchelvam et al., *The Journal of Neuroscience*, 2000, 20:9207-9214)

The interactive effects of multiple toxicant exposures have been examined in several other studies supported by the NIEHS. These include a study of the potential for dithiocarbamate (DTC) pesticides to influence the degree of neurotoxicity in a PD mouse model based on exposure to the herbicide paraquat. The group demonstrated that some commercially available DTCs can increase both the accumulation of dopamine in test-tube preparations of nerve cell connections and of paraquat in the brains of intact animals. The work suggests that selective DTCs may alter the cellular impact of different chemicals to enhance their neurotoxicity (Barlow et al., *Journal of Neurochemistry*, 2003, 85:1075-1086). Because the data from combined exposures may more accurately simulate "real-world" applications of these chemicals, these studies provide strong support for an environmental link to PD.

Another emerging focus of neurotoxicant research supported by the NINDS and the NIEHS is the role of early life exposures in the development of PD. A number of animal studies have demonstrated that prenatal exposure to these toxicants can produce an increased susceptibility much later in life to some of the agents that have been identified as risk factors for PD. These studies support the idea that PD may involve the cumulative effect of multiple insults over time.

Collaborative Centers Program

Although the evidence implicating environmental toxicants in PD continues to accumulate, the discussion above illustrates that genetic variability and mutations also play an important role. In order to more fully explore and accelerate research on the role of gene-environment interactions in the development of PD, NIEHS

released an RFA for Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER), and awarded funds to three Centers in September 2002.

CCPDER investigators meet annually and include NINDS staff to facilitate information exchange between the CCPDER and NINDS-supported Udall Centers (which co-exist at two research institutions). The lay community also participates through the External Advisory Boards of each Center and a collaborative CCPDER website intended to facilitate information exchange with the PD scientific and lay communities.

During their first two years of operation, each Center has made significant contributions to PD research, and investigators have benefited from the collaborative environment provided by the Centers Program. As examples, these collaborations have provided an important stimulus for the development of a PD registry in California, and have fostered the refinement of important animal models based on toxicant exposures. In addition to these natural collaborative activities among the different Centers, additional cross-Center interactions have been facilitated directly through supplemental funds provided by the NIEHS. To date, these funds have been used to support the development of an Epidemiology PD Consortium, which will help consolidate the diagnostic and exposure assessment methods used in epidemiology studies.

Stem Cells Continue to Show Promise

"Transplantation strategies based on stem cells present enormous potential, but we must better understand the fundamental biology of stem cells before they can safely and effectively be used for therapy of Parkinson's disease." – The Parkinson's Disease Research Agenda

For people with advanced PD, replacing the dopamine producing brain cells destroyed by the disease may be the best hope. Experiments in animal models of Parkinson's are progressing toward that goal. Recently, an NINDS-funded research team transplanted neural progenitor cells derived from human embryonic stem (ES) cells into rats with experimental PD and found that the animals improved on four different behavioral tests. The cells survived, stopped proliferating, and did not show tumors, but relatively few of them specialized to form dopamine cells. Another research group has demonstrated considerable success in deriving dopamine cells from human embryonic stem cells in culture, which holds promise both for transplantation and for studying these crucial cells to find what makes them vulnerable. (Ben-Hur T. et al., *Stem Cells,* 2004, 22(7):1246-55; Perrier A.L., et al., *PNAS,* 2004, 101:12543-8)

NINDS-supported researchers have also demonstrated that transplantation of mouse dopamine nerve cells derived from somatic cell nuclear transfer (SCNT) can help treat a PD-like condition in mice, the first time SCNT has been used for a brain disorder. In SCNT, the nucleus from an adult cell is transferred to an egg cell, which then forms stem cells that generate cells which can be used therapeutically. The team developed techniques to quickly and efficiently direct mouse stem cells to form several types of specialized brain cells that are potentially relevant for subsequent laboratory studies in cell cultures and animal models of PD. These studies may ultimately be useful in understanding the biological basis of Parkinson's. (Barberi et al., *Nature Biotechnology*, 2003, 21(10):1200-1207)

Other NINDS-funded researchers have also obtained similarly encouraging data by transplanting low doses of mouse embryonic stem cells into an area of the rat brain that has been implicated in PD. They found that these cells could successfully develop into dopaminergic neurons, integrate with the host tissue, and reverse asymmetric motor deficits characteristic in at least one type of rodent PD model. The use of low doses of cells was believed to play an important role in the ability of the cells to develop into neurons. It is important to note that some transplanted cells grew into uncontrolled tumors, illustrating the need for more research before embryonic stem cell transplantation clinical trials are considered in humans. (Bjorkland L.M. et al., *PNAS*, 2002, 99:2344-9).

Researchers are also exploring the potential of adult stem cells, and have isolated cells from the white matter of human brain (removed for therapeutic surgery) that can multiply and specialize to form the major cell types of the brain, both nerve cells and supporting cells. These "multipotential progenitor cells" are apparently abundant but restricted from forming nerve cells by their local environment. Once removed to cell culture or transplanted elsewhere in the brain, the cells can multiply and form new nerve and other cells. Understanding how local environmental influences determine the fate of progenitor cells is emerging as a major focus of stem cell biology. (Bunes et al., *Nature Medicine*, 2003, 9:439-47)

Intramural investigators at NINDS are also continuing to explore ways of transforming embryonic stem cells into dopamine neurons for possible transplantation. In past studies, these researchers obtained promising results with mouse embryonic stem cells, demonstrating that by driving a specific pathway of gene expression and applying other specific chemical signals, these cells can be influenced to develop into dopaminergic neurons in culture. When transplanted into a rodent model of PD, the cells appear to survive, integrate with the host

tissue, and reverse some motor impairments. (Kim et al., *Nature*, 2002, 418: 50-56)

This intramural work continues, in part to gather information on the federally-approved human ES cell lines in order to determine how they differ from the better understood mouse ES cells. For example, there are clear differences between human and mouse ES cells that make it difficult to predict the developmental potential of the human cells. However, recent work from several groups suggests that the developmental fates of human ES cells can be controlled in the laboratory, and that useful cell types can be produced. Ultimately, though, the therapeutic value of human ES cells will depend on generating large number of cells, in addition to directing their development to the appropriate fate.

NIH Stem Cell Characterization Unit

The many potential uses of human ES cells have prompted national research agencies in several countries to stimulate the rapid development of this field. In the U.S., NIH has awarded support to many universities to stimulate the use of the federally-approved human ES cell lines. In addition, the NIH has established a group – the NIH Stem Cell Characterization Unit – at the Bethesda campus to acquire federally-approved human ES cells from multiple sources and compare their properties. Different groups have used a variety of techniques to generate these cell lines, and as a result, the cells are difficult to grow. To address this issue, a central function of the NIH facility is to define general strategies that allow these cells to be widely and confidently used in research. The NIH stem cell facility now has 20 of the 22 federally-approved lines and cell stocks have been established for many of these lines. The supplier's original protocols (used to maintain individual cell lines) have now been replaced with a universal protocol that researchers can use (with minor modifications) to grow all of the lines. In addition, embryonic stem cells readily differentiate, making the undifferentiated cells hard to sustain. However, researchers have also established simple tests to identify cells in this undifferentiated state. Like other cells, ES cells are living organisms and can develop genetic alterations over time, and the ability to isolate new strains or sustain the parent strain depends on growing consistent stocks derived from a single cell. The Unit has now developed procedures to analyze the integrity of the genome in these cell lines. To provide information on all of these developments to investigators around the country, the Unit has established a website at:
http://stemcells.nih.gov/research/NIHresearch/scunit/.
To complement their cell characterization activities, the Unit has also established collaborations with other NIH intramural labs, and has provided human ES cells

to advanced courses attended by scientists from many countries.

New Research Capabilities: Necessary Tools for Research Progress

In the PD Research Agenda, the NIH recognized that a number of new research tools were needed across the PD research community. NIH staff has significantly improved community access to tools that were already available at the start of the Agenda, and has funded the development of new tools as well.

Array Technologies
"Gene array technologies allow simultaneous monitoring of the activity of thousands of genes. Methods are also becoming available to track the protein components of a cell. Researchers studying Parkinson's disease should apply these methods to understand, at the molecular level, the causes and progression of disease and the responses of neurons to treatment." – The Parkinson's Disease Research Agenda

NINDS and NIMH have established a consortium of three centers – at the Translational Genomics Research Institute, Duke and UCLA – to provide their investigators with the opportunity to further their research through the use of gene expression profiling technology. The primary goal of this consortium is to further basic and translational research through acquisition and dissemination of high quality expression array data. To date, researchers using the consortium have completed five projects on PD, and a sixth is in progress. The data from experiments performed by the NINDS/NIMH Microarray Consortium are shared publicly via a website (http://arrayconsortium.tgen.org) six months after a study is completed.

In addition, NINDS has provided administrative supplements to researchers to access microarray technology through two separate program solicitations. In response to these announcements, NINDS awarded six supplements with relevance to PD. The Institute has also funded a study using microarrays through a joint RFA with NIA on collaborative studies on AD and other neurodegenerative conditions.

Models of Parkinson's Disease
"Present models do not adequately mimic the cause or clinical course of human Parkinson's disease, the gradual cell loss, or the destruction of non-dopamine cells. A range of models from in vitro molecular and cellular models through

simple organisms like fruitflies and nematode worms, to transgenic mice and primates is needed." – The Parkinson's Disease Research Agenda

Thanks to the remarkable developments in PD genetics and cell biology, the past five years have been a period of explosive growth in the development of animal models of PD. In addition to producing a number of animal models by manipulating the genes for alpha-synuclein and parkin (described in earlier sections of this report), researchers have also developed models through manipulation of intracellular pathways. For example, researchers at NIDA's intramural research program developed a strain of genetically-engineered mice with a tissue-specific disruption of mitochondrial function in dopamine neurons. These animals display major pathophysiological features of PD. Several lines of evidence suggest that disturbances in the cellular "respiration" that occurs in mitochondria is involved in the development of PD, and this finding adds further credence to this view. In addition, exposure of experimental animals to a variety of agricultural toxicants (also described in more detail in the above sections) can also yield informative models of PD. NINDS and the NIH are committed to enhancing the sharing of these models between laboratories, and to this end, have established a repository at UCLA to facilitate the distribution of mouse models to the research community (see below for more details).

NCRR supports the study of non-human primate models of PD through its National Primate Research Centers. For example, at the NCRR-supported Wisconsin National Primate Research Center, the PD program combines expertise and resources in neuroimaging, neurobiology, and transplantation therapies. Current research and clinical activities include production of chemically-induced PD in rhesus monkeys, transplantation of neural tissue, deep brain stimulation therapy, physiological study of circuits that malfunction in PD, and positron emission tomography imaging of the brain.

Neuroimaging

"At present the most developed biomarkers for Parkinson's disease rely upon neuroimaging. Beyond biomarkers, there is a wide spectrum of imaging methods that may yield insights into the causes and treatment of this disease." – The Parkinson's Disease Research Agenda

As a first step to explore the use of imaging tools as biomarkers in PD, NINDS sponsored a workshop in July 2003 to consider the use of imaging as an additional measure or endpoint in clinical trials; the capabilities of current imaging technology, including molecular "tags;" and the feasibility of using imaging measures consistently in multicenter clinical trials. Following this meeting, the

participants and NINDS staff published a paper which outlines recommendations on: 1) methodological changes in studies to determine how imaging measures relate to clinical endpoints, and 2) development of new markers to better capture the degenerative process and more of the clinical features of PD (Ravina et al., *Neurology*, 2005, 64:208-215).

In addition, through the NCRR General Clinical Research Centers (GCRC) program, researchers at the Long Island Jewish Research Institute in New York are using positron emission tomography imaging to identify changes in metabolism in the brains of patients with PD, and to correlate these metabolic changes with symptoms of the disease.

Brain Banks and Other Repositories

"The systematic collection, maintenance, and distribution of biological and clinical materials would contribute substantially to advancing basic and clinical research on Parkinson's disease."– The Parkinson's Disease Research Agenda

Several years ago, NINDS recognized that for many neurological conditions, a repository of DNA samples, immortalized cell lines, and accompanying clinical and pedigree data would be an invaluable resource. Beginning with a contract award in September 2002, the NINDS has supported a repository for DNA and genetic material at the Coriell Institute for Medical Research in Camden, New Jersey. Although the repository is currently storing samples from individuals with parkinsonian conditions, stroke, epilepsy, and motor neuron diseases, the contributions of the PD research community have been the highlight of the resource to date. Of more than 4000 samples submitted, 2231 are from PD researchers, including 600 PD samples available for sharing now, and approximately 250 control subject samples. Additionally, NINDS has recently made plates (or panels) of DNA samples available to researchers, which will allow them to perform rapid screens for validating known genes and/or for discovering new genes. One of the available plates contains 92 samples from well-characterized Caucasian individuals with late onset PD (who meet the stringent UK (London) Brain bank criteria for PD); the other contains samples from age and gender-matched controls.

In addition to the need for human material for study, NINDS has also recognized the burden placed on investigators by the financial and logistical realities of distributing other high demand research resources. Accordingly, NINDS and the University of California at Los Angeles created a resource in FY 2003 that will distribute PD mouse models that are not available through other resources such as Jackson Laboratories. NINDS sent a letter in October 2003 to approximately 2500

researchers to strongly encourage contributions to this resource. Models presently available in the repository include a knockout model of the DJ-1 gene, developed by NIMH and recently implicated in familial PD; and two models of the alpha-synuclein form of familial PD, generated by NHGRI.

NCRR's Division of Comparative Medicine also supports mutant mouse models for the study of PD and related diseases through its animal resource programs. The Induced Mouse Resources Program and the Mutant Mouse Regional Resource Centers maintain several mouse strains with applications to PD research.

Udall Centers: Data Organizing Center Created

"...the ultimate goal of improving the integration of centers is to create a patient-centric system in which community physicians, research centers, and NIH are all part of a cohesive network. With such a system, information on patients can be better captured and managed, and research can be integrated at both the basic and clinical levels." – The Parkinson's Disease Matrix

In July 2002, mid-way through the PD Research Agenda, NIH held a PD Coordination Summit with leading scientists and clinicians to explore roadblocks that were impeding PD research. Participants suggested that better integration of the Udall Center program could accelerate their progress. Accordingly, the group suggested that formal coordination of Centers' data was needed, with a definite focus on the capture of clinical information.

To more specifically define the needs of the Udall Centers and other PD research centers, and to develop a minimum data set for both the clinical and pathological diagnosis of PD, NINDS sponsored a workshop in March 2003. Outside researchers, Udall center directors, and NIH staff discussed ways in which PD research centers could be more collaborative, and how the collection of PD data and resources could be streamlined. Two working groups were assigned to the tasks of developing a minimum clinical data set for use in clinical studies, and a minimum pathological data set, the standardized collection of PD tissues by coordinated research centers. NINDS made these initial minimum data sets for the capture of clinical and pathological diagnostic information freely available on the NINDS PD website shortly after the meeting.

As the next step, NINDS solicited applications for the first Parkinson's Disease Data Organizing Center (PD-DOC), and awarded this cooperative agreement to the University of Rochester in September 2004; funding for this award is also

being provided by NIEHS. The Center is intended to serve as a 'data clearinghouse' for the Udall Centers program, the CCPDERs, and other Parkinson's research centers. The PD-DOC will collect clinical data on PD patients for research use and sharing by the community, as well as create virtual catalogs of biological materials of interest to PD.

Since the award was made, the PD-DOC has explored ways to dovetail the University of Rochester's databasing efforts with the existing NINDS genetics repository, and has begun to create patient confidentiality forms to ensure the protection of PD patients whose data will be collected. Udall representatives and others from the previous working group continue to evaluate and revise the set of clinical data elements previously developed by the Institute. The PD-DOC investigators have also begun initial contacts with the VA to determine if any commonalities could be taken advantage of, given their similar efforts on data banking. In December 2004, the PD-DOC investigators presented their strategy and plans at the 6th annual Udall Centers meeting, to collect additional feedback from the Center Directors and Staff.

Planning for the Future

As the PD Research Agenda draws to a close, NIH staff is already actively planning a second PD Coordination Summit, to be held June 6-7, 2005. Although the plans for this Summit are still preliminary, NIH is committed to providing an opportunity at this meeting for the leaders of the PD voluntary community to voice their recommendations and concerns to the NIH and to the scientific and clinical participants. The overall goal for this meeting is to develop research recommendations for the NIH, including any revisions of or additions to the PD Matrix goals which were derived from the first Coordination Summit held in July 2002.

Conclusions

The research highlights above offer only a very small snapshot of the breadth of the research on PD that NIH is conducting. However, they do illustrate the significance of many of the scientific findings made since the start of the PD Research Agenda, and the impact of programmatic actions taken to date. Although scientists have not yet developed a cure for PD, they have pushed the field forward in many directions – all of which will contribute to the eventual development of therapies. NINDS will continue to lead the efforts of NIH in PD

research beyond the Agenda towards this goal – utilizing the PD Matrix goals and other recommendations made by the scientific community at the June 2005 planning meeting to guide future program actions, from basic science initiatives to clinical trials.